The effect of comedication with a csDMARD on drug retention and clinical effectiveness of anti-TNF therapy in patients with axial spondyloarthritis

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Abstract: Objective To explore the effect of comedication with conventional synthetic disease modifying antirheumatic drugs (csDMARDs) on drug retention and clinical effectiveness of tumour necrosis factor inhibitors (TNFi) in patients with axial spondyloarthritis (axSpA). Methods Inclusion of all patients starting treatment with a TNFi in a large prospective axSpA cohort (SCQM-axSpA). Crude drug retention was analyzed using the Kaplan Meier method and in adjusted analyses we used Cox proportional hazard regression to model TNFi discontinuation. We evaluated multiple disease activity measures and validated clinical response criteria over time. Results A total of 2765 TNFi treatment courses were included from 1914 axSpA patients, with 20.4% in combination with a csDMARD. In unadjusted analyses, the monotherapy group had significantly shorter median TNFi retention time (32.7 months), compared to the co-therapy group (39.1 months) (p= 0.04). In multivariate adjusted analyses, the monotherapy group had significantly lower TNFi retention, with a hazard ratio (HR) of 1.17 (95%CI: 1.01;1.35). This effect was even larger when considering only Infliximab treated patients, with a HR for monotherapy of 1.36 (95%CI: 1.06;1.74). Clinical response rates were almost identical at 1 year with a change in the Bath Ankylosing Spondylitis Disease Activity Index of -2.02 and -2.00 (p=0.83) and a change in the Ankylosing Spondylitis Disease Activity Score using CRP of -1.14 and -1.12 (p=0.45) in the monotherapy and co-therapy groups respectively. Conclusion We demonstrate an association between the combination of a TNFi with csDMARDs and improved drug retention in axSpA patients, particularly in the subgroup of patients with Infliximab.

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The effect of comedication with a csDMARD on drug retention and clinical effectiveness of anti-TNF therapy in patients with axial spondyloarthritis.

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ABSTRACT

Objective

To explore the effect of comedication with conventional synthetic disease modifying antirheumatic drugs (csDMARDs) on drug retention and clinical effectiveness of tumour necrosis factor inhibitors (TNFi) in patients with axial spondyloarthritis (axSpA).

Methods

Inclusion of all patients starting treatment with a TNFi in a large prospective axSpA cohort (SCQM-axSpA). Crude drug retention was analyzed using the Kaplan Meier method and in adjusted analyses we used Cox proportional hazard regression to model TNFi discontinuation. We evaluated multiple disease activity measures and validated clinical response criteria over time.

Results

A total of 2765 TNFi treatment courses were included from 1914 axSpA patients, with 20.4% in combination with a csDMARD. In unadjusted analyses, the monotherapy group had significantly shorter median TNFi retention time (32.7 months), compared to the co-therapy group (39.1 months) (p= 0.04). In multivariate adjusted analyses, the monotherapy group had significantly lower TNFi retention, with a hazard ratio (HR) of 1.17 (95%CI: 1.01;1.35). This effect was even larger when considering only Infliximab treated patients, with a HR for monotherapy of 1.36 (95%CI: 1.06;1.74). Clinical response rates were almost identical at 1 year with a change in the Bath Ankylosing Spondylitis Disease Activity Index of -2.02 and -2.00 (p=0.83) and a change in the Ankylosing Spondylitis Disease Activity Score using CRP of -1.14 and -1.12 (p=0.45) in the monotherapy and co-therapy groups respectively.

Conclusion

We demonstrate an association between the combination of a TNFi with csDMARDs and improved drug retention in axSpA patients, particularly in the subgroup of patients with Infliximab.

MANUSCRIPT

The efficacy of tumour necrosis factor inhibitors (TNFi) in the management of ankylosing spondylitis (AS), in patients for whom treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is inadequate, has been clearly demonstrated in numerous randomised controlled trials (RCT) (1-5). The combination of a TNFi with a conventional synthetic disease modifying antirheumatic drug (csDMARD) such as Methotrexate (MTX) is undeniably associated with a lower risk of TNFi discontinuation compared with TNFi monotherapy in rheumatoid arthritis (RA) (6). In psoriatic arthritis (PsA), improved TNFi retention has been described when associated with csDMARDs (7-10), although several RCTs did not demonstrate any advantage of co-therapy with MTX in terms of clinical efficacy (11-12). The majority of registry studies and pharmacokinetic studies of AS patients have not demonstrated any benefit of csDMARD therapy in association with TNFi (7, 13-16), although a recent publication from the ARTIS cohort reported better 5-year drug retention with a first TNFi when given in combination with a csDMARD(17).

Although the majority of axial spondyloarthritis (axSpA) patients respond very well to TNFi, up to 40% fail to reach an acceptable level of clinical efficacy (18-19). One possible explanation could be the formation of TNFi-neutralizing antibodies which may decrease serum drug levels and subsequently result in loss of efficacy. Alternatively, other pathogenic mechanisms or cytokine pathways, besides TNF, may also be involved. Concomitant use of csDMARDs such as MTX may improve the efficacy of TNFi by targeting other pathways and reducing immunogenicity, thus preventing secondary loss of efficacy. This is of particular significance in axSpA, as there are fewer classes of biologic agents to switch to in the event of treatment failure, in comparison with RA. Observational data from registries reveal a high frequency of csDMARD use, both as monotherapy and in combination with TNFi in AS patients, with rates of up to 61% (20-22).

One striking difference between axSpA and RA is that csDMARDs are clearly effective as monotherapy in RA, whereas their efficacy as monotherapy has not been demonstrated in axSpA (23-25). Current international Assessment of SpondyloArthritis international Society (ASAS) / EUropean League Against Rheumatism (EULAR) recommendations do not suggest any role for csDMARDs in patients with axSpA when used in combination with TNFi (26-27). Several European Rheumatology societies suggest a potential role for immunosuppressive therapy (without precision of which agent) in the treatment of AS patients taking Infliximab (IFX), with the rationale of preventing or reducing the development of anti-IFX antibodies (28).

Thus, despite the lack of convincing evidence for a role for csDMARDs in combination with TNFi in patients with axSpA, a large percentage of physicians continue to prescribe this combination. Therefore, we sought to further explore evidence for a potential benefit of csDMARDs in combination with TNFi in patients with axSpA in a large prospective cohort.

Patients and methods

Study population and design

The "Swiss Clinical Quality Management" (SCQM) registries monitor disease activity, radiographic damage, patient characteristics and various symptom questionnaires at regular intervals in patients with RA, axSpA, PsA and undifferentiated arthritis Inclusion of patients into the database is based on expert attending Rheumatologist opinion. Clinical and laboratory data are collected annually with the possibility to include additional data at intermediate visits (29). Ethical approval for the collection of patient data was given by the national review board. Informed consent was obtained from all patients at inclusion in the registry. Management decisions after inclusion into SCQM were left entirely to the discretion of the treating rheumatologist.

AxSpA patients recruited in the ongoing SCQM registry are required to have a clinical diagnosis of AS or another form of SpA with predominantly axial disease according to the treating rheumatologist (30). Patients with psoriatic arthritis, including those with axial involvement are included in a separate cohort. This was a longitudinal study within the SCQM-axSpA cohort analyzing data collected between January 2005 and August 2013.

The following minor modifications were required as the cohort was initiated prior to publication of the ASAS criteria: the ASAS criterion " inflammatory back pain" was defined as low back pain and morning stiffness for >3 months, improving with exercise but not relieved by rest, as well as age at onset <45 years. Furthermore, the ASAS criterion "good response to NSAIDs" was only added to the questionnaire in 2009. Inclusion criteria included the initiation of a TNFi after recruitment into the cohort (or within a month prior to inclusion in the registry) and at least one follow-up visit on the respective TNFi. Exclusion criteria included TNFi initiation more than 1 month prior to inclusion in the registry and missing follow-up assessments.

Outcomes and exposures

The study's predefined primary outcome of interest was the rate of TNFi retention of combined therapy with csDMARDs and TNFi agents (co-therapy), compared with TNFi monotherapy. The

exposure of interest was the presence or absence of concomitant csDMARD use at baseline (BL) in association with the TNFi. Secondary outcomes of interest were the longitudinal evolution of disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (31) and the Ankylosing Spondylitis Disease Activity Score using CRP (ASDAS-CRP) (32) after initiation of a TNFi. The following clinical response variables were also assessed at 12 months: 50% improvement in the BASDAI (BASDAI50), ASDAS inactive activity (ASDAS-ID), ASDAS clinically important improvement (ASDAS-CII) and the ASAS criteria for 20% and 40% improvement (ASAS20 and ASAS40) (29). We explored potential effect modification by the type of TNFi (infliximab versus humanized TNFi), presence of positive classification criteria (Modified New York Criteria (MNYc) and ASAS axSpA criteria), smoking and the presence of peripheral joint involvement. Response outcomes based on the proportion of patients adhering to TNFi therapy, according to the LUND Efficacy indeX (LUNDEX) were also calculated (33).

Statistical analysis

All analyses were planned a priori and no correction for multiple testing was performed. Regarding the baseline characteristics, categorical variables were compared between patients with TNFi as monotherapy and patients treated with one or more csDMARDs in association with a TNFi using the Chi-squared test. We utilized standard descriptive statistics to test for differences in mean values. In the cases with non-symmetrically distributed variables, the Mann-Whitney test was utilized. All tests were two-sided, with a significance level set at 5%.

We chose TNFi retention as the primary outcome as drug retention rates indicate both the patient's and the doctor's satisfaction with therapy and provide a global measure of the overall treatment effectiveness and tolerability. The Kaplan Meier method was utilized to obtain the graphical representation of drug discontinuation over time. In adjusted analyses, we used Cox proportional hazard regression to model TNFi discontinuation with adjustments for potential confounders (age at baseline, sex, disease duration at baseline, education level (as a proxy of socio-economic status), presence of ASAS axSpA classification criteria, elevated CRP at baseline, smoking status, calendar year initiation of TNFi (<2008, > 2011) and number of TNFi used). Andersen-Gill Cox models were utilized to account for multiple TNFi discontinuations in the same patient.

We investigated effect modification for positive MNYC, positive ASAS criteria, the presence of peripheral joint involvement and smoking in terms of monotherapy versus co-therapy. In addition, sensitivity analyses with the different classification criteria (Rheumatologist diagnosis, MNYC and ASAS) were performed.

The baseline visit was defined as an available visit within 3 months prior to TNFi initiation and up to 1 month following the start of the TNFi agent. When clinical outcome measures were unavailable at 12 months (+/- 3 months), we used longitudinal interpolation with mixed-effects linear regression to impute missing values. This imputation was required by the structure of SCQM data, as the yearly control visit does not necessarily match yearly intervals after initiation of treatment. A mixed-effects model for longitudinal data was used to analyze disease activity (BASDAI and ASDAS-CRP) over time. Mixed-effects models with per patient random intercept and random slope were used to analyze BASDAI50, ASDAS-CII, ASDAS-ID and ASAS20/40. Adjustments were made for potential confounders as described above. Stata statistical software (StataCorp LP, version 11.1) was used for all analyses.

Results:

Patient disposition and characteristics

A total of 1914 axSpA patients were included in the analyses for a total of 2765 TNFi treatment courses (Table 1). At baseline 55.3% were males with a mean age of 41.7 years (+/- 12.0), a median disease duration of 8.3 years [IQR: 3.0, 15.9] and a median follow-up of 5.0 years [IQR: 2.8, 7.3]. A total of 565 (20.4%) of the TNFi treatment courses were as co-therapy with a csDMARD (MTX 77.2%, Sulfasalazine (SSZ) 21.2%, Leflunomide (LEF) 8.3% and other csDMARDs 1.6%). The mean MTX dose was 13.6 mg (SD 5.0) per week and the mean SSZ dose was 1.8 g (SD 0.5) per day. The TNFi prescribed was infliximab (IFX) in 26.1%, adalimumab (ADA) in 33.3%, etanercept (ETN) in 27.5%, golimumab (GOL) in 12.3% and certolizumab pegol (CER) in 0.8%.

Co-therapy patients were less likely to be HLA-B27 positive (62.1% vs. 67.0%, p=0.046), more likely to present with peripheral joint manifestations (72.2% vs. 52.7%, p<0.001), less likely to be ASAS criteria positive (65.3% vs. 80.6%, p<0.001) and had a longer median follow-up (6.0 vs. 4.7 years, p<0.001). In addition, co-therapy patients were significantly more likely to be treated with IFX and significantly less likely to be treated with ADA, ETN or GOL. At 12 months, 62.0% of the co-therapy group remained on a csDMARD and 10.8% of the monotherapy group had commenced a csDMARD. There was a significant reduction in the use of csDMARD co-therapy in the overall cohort over the 3 time-periods of prior to 2008, 2008-2011 and after 2011, of 26.2%, 20.3% and 14.5% respectively.

Drug retention

In unadjusted analyses of all TNFi treatment courses, the median TNFi retention time was 33.9 months. There was a significantly longer median TNFi retention time in the co-therapy group, compared with the monotherapy group (39.1 months versus 32.7 months respectively, p=0.04).

When considering only the first TNFi treatment course, the median TNFi retention time was 36.3 months. Regarding drug retention in patients treated with IFX, there was a significant difference between the co-therapy and the monotherapy groups, with median TNFi retention times of 51.9 months and 30.4 months respectively (p=0.02). No significant differences were demonstrated with the other TNFi.

In multiple adjusted analyses corrected for potential confounding factors, we found a significantly shorter TNFi retention in monotherapy patients with a HR of 1.17 (95%CI: 1.01; 1.35) (Figure 1A). When considering only IFX patients, there was an even greater benefit of co-therapy with regards to TNFi retention with a HR for monotherapy of 1.36 (95%CI: 1.06; 1.74) (Figure 1B), which was not apparent with the other TNFi.

Significant predictors for greater TNFi retention were male sex (p<0.001), the presence of positive ASAS criteria (p=0.03), raised CRP levels at baseline (p=0.008) and shorter disease duration at baseline (p=0.009). There was no evidence of effect modification in terms of monotherapy versus co-therapy for positive MNYC, positive ASAS criteria or peripheral joint involvement. However, there was effect modification with regards to smoking (HR 0.72, 95%CI: 0.54; 0.97). The TNFi retention advantage with co-therapy was lost in smokers, whereby non-smokers with co-therapy had a significantly greater TNFi retention than smokers with co-therapy (p=0.003) (Figure 2). The previously described improved TNFi retention with csDMARDs in patients treated with IFX was not observed in the subgroup of current smokers treated with IFX.

The sensitivity analyses restricting the sample to patients fulfilling the ASAS criteria revealed very similar hazard ratios, whereby the monotherapy group demonstrated a strong trend towards lower TNFi retention with a HR of 1.22 (95%CI: 0.99; 1.51) for all patients, and a HR of 1.35 (95%CI: 0.97; 1.88) in the subgroup of patients treated with Infliximab.

Regarding the reasons for TNFi discontinuation, there were no significant differences between the monotherapy and co-therapy groups (p = 0.20), particularly with regards to adverse events (24.3% and 25.0% respectively) (Table 1). Although, there was a slightly higher (non-significant) rate of remission in the combination group (5.9% vs. 3.2%).

Clinical response rates

There were no significant differences between the monotherapy and co-therapy groups with regards to change in BASDAI score over the first year (p=0.83), nor with change in ASDAS-CRP scores over the

first year (p=0.45) (Table 2). This effect remained constant in specific sub-groups (ASAS positive, MNYc positive, non-radiographic axSpA (nr-axSpA), first TNFi only, IFX patients and patients with peripheral involvement) (Table 2). Overall, patients with their first TNFi and patients with positive MNY or ASAS criteria demonstrated greater improvements in BASDAI and ASDAS-CRP scores, whereas patients with nr-axSpA responded less well.

We found no significant differences between the monotherapy and co-therapy groups with regards to BASDAI50, ASDAS-CII, ASAS20 and ASAS40 at 1 year (Table 3). However, more patients in the monotherapy group obtained an ASDAS-ID (15.1% vs. 9.5%, p=0.01) than in the co-therapy group. When we adjusted the ASDAS-ID response outcomes by the proportion of patients adhering to TNFi therapy, according to the LUNDEX, the differences between groups were less pronounced (Table 3).

In the subgroup of patients treated with IFX, the majority of the clinical outcome variables were numerically superior in the co-therapy group compared to the monotherapy group, and the ASDAS-CII was significantly greater in the co-therapy group (60.5% vs. 49.3%, p=0.02). In ASAS positive IFX-treated patients, there was a significantly greater improvement in the ASDAS-CRP in the co-therapy group compared with the monotherapy group (-1.30 vs. -1.14, p=0.040). We repeated the analyses investigating clinical outcomes at 24 months and found that the change in BASDAI was -1.839 in the monotherapy group and -1.837 in the co-therapy groups (p=0.97).

Discussion

This longitudinal study of a large cohort of patients with axSpA demonstrates improved TNFi retention in patients treated with csDMARDs in combination with the TNFi. The overall survival advantage appears to be uniquely due to a benefit in the subgroup of patients treated with IFX.

A potential benefit for the use of csDMARDs in association with TNFi in axSpA has been hypothesized due to an established benefit in RA patients and a possible reduction in anti-TNF antibody formation. An independent anti-inflammatory effect of the csDMARD in AS appears not to exist, at least not for MTX, which has been evaluated in three RCTs, with a Cochrane review concluding that there was "not enough evidence to support any benefit of MTX in the treatment of AS" (23).

A reduced clinical response to IFX treatment in AS patients has been demonstrated to correlate with the formation of anti-IFX antibodies (34). In PsA patients, Fagerli et al found a significant benefit of MTX in combination with IFX in terms of TNFi drug retention, but not with ADA or ETN (9). In another study of PsA patients, there was no benefit of MTX in combination with ETN (35). In axSpA patients

from the Czech ATTRA cohort, no benefit was observed with csDMARDs given in combination with ADA with regards to either drug retention or the probability of reaching low disease activity (36).Conversely, Lie et al found a significant advantage in terms of TNFi retention with MTX co-therapy in ADA, ETN and IFX-treated AS patients, but no difference with regards to undifferentiated SpA for all 3 agents (17).

In contrast to the drug retention data, the co-therapy group did not demonstrate any advantages over TNFi monotherapy in terms of clinical effectiveness. Obviously drug retention reflects a combination of efficacy and tolerability, as well as patient and practitioner preferences. One possible explanation for this discrepancy is that patients on concomitant csDMARDs present fewer TNFi-related side-effects resulting in improved drug retention without demonstrating a significant benefit in terms of clinical effectiveness. Nevertheless, we found no significant differences between the 2 groups with regards to the reasons for TNFi discontinuation, including adverse events.

A systematic review of RCTs and observational studies of TNFi plus MTX versus TNFi monotherapy in patients with PsA was recently conducted (37). The results from the RCTs did not find any differences in efficacy for peripheral joint disease. Similarly, data from three European biologics registries did not demonstrate any major differences in efficacy, although there was evidence of benefit with regards to TNFi drug survival for patients on combination therapy.

Another potential explanation for difference between outcomes is that drug retention is measured over time, while the clinical response rates were measured at 1 year. The 1 year mark was chosen as the majority of improvement in the clinical response variables occurred during the first 12 months with little change thereafter. Nevertheless, we repeated the analyses investigating clinical outcomes at 24 months and the results were quantitatively similar. The decision to cease TNFi therapy because of clinical inefficacy or an adverse event in this observational study was at the discretion of the treating rheumatologist and was not subject to study protocol. It is therefore unlikely that there was any bias in the way such decisions were made between the 2 treatment groups.

A significantly higher proportion of patients obtained the ASDAS-ID outcome in the monotherapy group compared with the co-therapy group. Although statistically significant, this small difference is unlikely to be clinically relevant. When the proportion of patients adhering to TNFi therapy was taken into account with the use of the LUND Efficacy indeX (ASDAS-ID LUNDEX) these differences disappeared.

The response rates of certain variables such as the ASAS40 were somewhat lower than those seen in other trials. Only 8% of patients in this cohort demonstrated a ≥ 40% improvement in BASFI scores at 1 year, which limited the ASAS40 response rates. This may be related to a relatively high age and long disease duration in our study population, as well as the inclusion of multiple TNFi treatment courses.

There are certain well known limitations to comparing treatment outcomes based on observational data, as the decision to treat patients is not entirely random, but is dependent upon numerous variables. Despite the fact that our results are very similar following correction for a large number of potentially confounding variables, the possibility remains of residual confounding by indication, which may have affected the response. There are a number of reasons why this seems unlikely. Firstly, the 2 groups were well matched in terms of age, sex, socio-economic status, disease duration, CRP and smoking status. Secondly, there were no significant differences between the groups in terms of disease activity, determined by the BASDAI and the ASDAS-CRP. Thirdly, there were differences observed in the proportion of patients in each group in terms of the specific TNFi prescribed, with patients more likely to be in the co-therapy group with IFX and more likely to be in the monotherapy group with ADA, ETN and GOL. Nevertheless, there is no convincing evidence that there is a difference in efficacy between the various TNFi, and thus this prescribing difference is unlikely to have had an effect on the outcomes.

Although the monotherapy and co-therapy groups were well matched, there were significant differences with regards to peripheral arthritis, HLA-B27 positivity and positive ASAS criteria. As the HLA-B27 status was unknown for 16.1% of treatment courses (15.4% of patients), this variable was not included in the initial model. We repeated the analyses including only patients with known HLA-B27 status and the results were quantitatively similar (data not shown).

In the overall population 77.6% of patients were ASAS criteria positive and 70.4% of patients were MNYC criteria positive. The ASAS criteria could not be determined for 22.2% of the treatment courses due to absent MRI or unknown HLA-B27 status. It is possible that these investigations were preferentially not performed in patients with a typical presentation of axSpA. If we assume that these patients with missing classification status were ASAS criteria positive, the overall rate of ASAS positivity increases to 82.6%, which is very similar to the 82.9% sensitivity of the ASAS classification criteria (38).

In order to determine whether the differences observed in TNFi retention between the 2 groups were due to the incomplete matching of several baseline variables, we performed propensity score

matching. We obtained two subgroups of 379 patients each that were better matched, in terms of peripheral arthritis, HLA-B27 positivity and the duration of follow-up (See Supplementary Table 1). In this propensity matched sample, the monotherapy group had a somewhat lower TNFi retention with a HR of 1.14 (95% CI: 0.93; 1.40), which is qualitatively similar to the HR of 1.17 demonstrated in the initial multiple adjusted analyses. The loss of statistical significance is probably due to the much smaller sample size resulting from this type of analysis. When including only those patients treated with infliximab, the HR was 1.47 (95% CI: 1.06; 2.03).

We defined the co-therapy group as those on at least one csDMARD at the time of TNFi initiation. Not taking into account the minority of patients that subsequently ceased the csDMARD is unlikely to have had an effect on our results. Indeed Lie et al reported that in sensitivity analyses of drug retention in patients with AS, there were similar results in those stopping the csDMARD at the time of TNFi introduction and those continuing the csDMARD (17).

There are a number of strengths to our current study. Our population originated from a national prospective cohort of patients with axSpA, and consequently, the outcomes reflect the experience of the patients themselves and of their rheumatologists, as they occurred. In many observational studies the classification criteria are not available, whereas we had this information for the majority of our patients. Many studies are limited to a subset of the axSpA population, such as those with MNYC or ASAS positive classification criteria. We investigated all subgroups, including those patients with nr-axSpA and those with consultant rheumatologist defined axSpA but missing imaging or HLA-B27 status. The fact that we demonstrated the same outcomes regardless of the classification utilized strengthens the robustness of these findings. No restrictions were made to our study population in terms of classification criteria or disease activity, so this cohort is truly representative of the group of patients that we see in our hospital based clinics and community-based consulting rooms on a daily basis (39).

Despite not having access to the percentage of patients in this cohort with positive CASPAR criteria, it is very unlikely that there were a significant number of PsA patients incorrectly classified as axSpA. Firstly, there is a separate cohort for PsA patients, and secondly, as the rate of a past or present history of psoriasis in our cohort was 10.9%, which is very similar to the rate of 9.3% found in a systematic review and meta-analysis of the prevalence of extra-articular manifestations in AS (40).

Moreover, we controlled for a large number of potentially confounding variables, including smoking (current and past), which has generally not been included in other cohorts. This is an important

point, as smoking has been shown to be associated with an impaired response to TNFi in axSpA (41). Indeed, we found that the TNFi retention advantage of combination with a csDMARD was absent in smokers, both in the overall cohort and in the subgroup of patients on IFX. There are reports suggesting that smoking increases basal metabolic rate and may reduce the potency of csDMARDs (42). This further emphasizes the importance of encouraging smoking cessation in axSpA patients. Finally, the fact that we demonstrate almost identical results with a propensity-matched sample and in sensitivity analyses limited to ASAS criteria positive patients, further reinforces the validity of our findings.

In conclusion, we demonstrate an association between co-therapy with a TNFi and csDMARDs and improved drug retention in axSpA patients. The overall survival advantage appears to be uniquely due to a benefit in the subgroup of patients treated with IFX. Regarding clinical effectiveness, co-therapy was not significantly superior to TNFi monotherapy. Higher rates of TNFi retention were seen in males and in patients with shorter disease duration, positive classification criteria and raised CRP levels. Consequently, there may be a role for the use of csDMARDs in axSpA patients treated with IFX, particularly in non-smokers.

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Table and Figure legends:

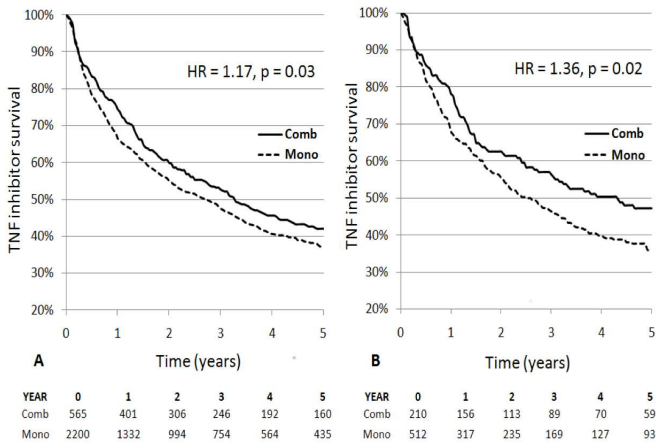
Figure 1. Adjusted TNF inhibitor retention curves for monotherapy (Mono) and co-therapy (Comb) groups using a Cox proportional hazard model; (A) for all patients and (B) for patients treated with Infliximab. The tables show the number of patients at risk at baseline (0), 1, 2, 3, 4 and 5 years in each group. HR = hazard ratio.

Figure 2. Adjusted TNF inhibitor retention curves for monotherapy (MONO) and co-therapy (COMB) groups in smokers and non-smokers using a Cox proportional hazard model. The p-value relates to non-smokers in the co-therapy group versus smokers in the co-therapy group.

Table 1. Baseline characteristics of patients with axSpA classified by treatment with TNFi monotherapy verses TNFi in association with a csDMARD (co-therapy) including all treatment courses. Except where indicated otherwise, values are the mean (± standard deviation). N = number. TNFi = tumour necrosis factor inhibitor; axSpA = axial spondyloarthritis; IQR = Inter Quartile Range; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using CRP (C-reactive protein) levels.

Table 2. Change in BASDAI and ASDAS-CRP scores after 1 year of treatment with TNFi in patients with axSpA classified by TNFi monotherapy versus co-therapy in the different subgroups. Mono = monotherapy (TNFi alone); Comb = Co-therapy (TNFi + ≥ 1 DMARD); BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using CRP (C-reactive protein) levels; TNFi = Tumor Necrosis Factor inhibitors; axSpA = axial spondyloarthritis; ASAS = Assessment of SpondyloArthritis international Society; MNYc = modified New York classification criteria for ankylosing spondylitis; nr-axSpA = non-radiographic axial spondyloarthritis; IFX = Infliximab.

Table 3. Response rates after 1 year of treatment with TNFi in patients with axSpA classified by TNFi monotherapy versus co-therapy including all treatment courses. Except where indicated otherwise, values are percentages. TNFi = Tumor Necrosis Factor inhibitors; axSpA = axial spondyloarthritis; LUNDEX = LUND Efficacy indeX; ASAS = Assessment of SpondyloArthritis international Society; BASDAI50 = 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASDAS-CII = ASDAS clinically important improvement; ASDAS-ID = ASDAS inactive disease; ASAS20 = 20% improvement according to ASAS; ASAS40 = 40% improvement according to ASAS.



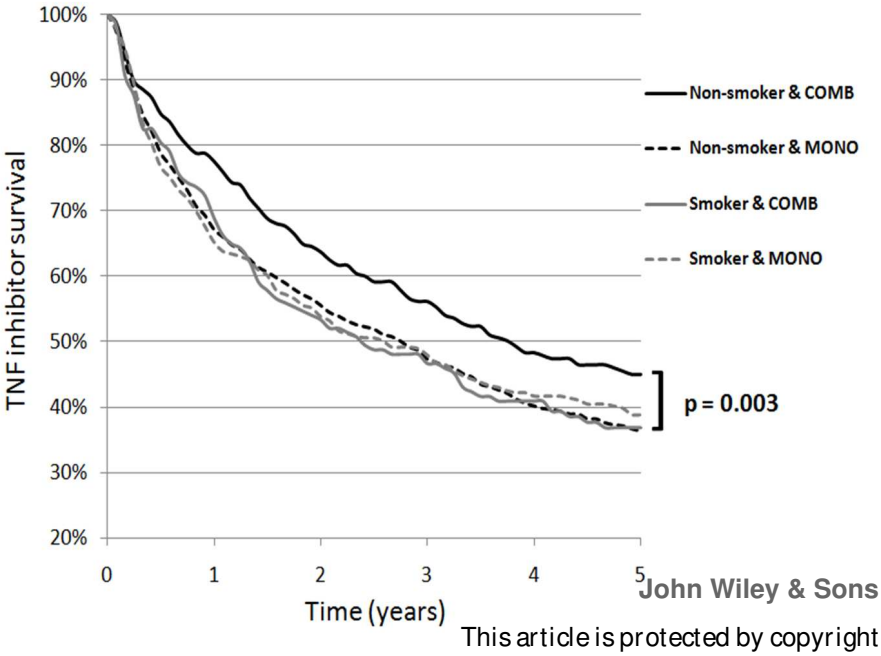


Table 1: Baseline characteristics of patients with axSpA classified by treatment with TNFi monotherapy verses TNFi in association with a csDMARD (co-therapy) including all treatment courses.

Characteristic	N	Monotherapy N=2200	Co-therapy N=565	p
Age (years)	2765	41.5 ± 11.9	42.5 ± 12.3	0.07
Gender (%, male)	2765	55.0	56.5	0.55
Weight (kg)	2611	74.0 ± 15.1	74.9 ± 16.0	0.20
Height (cm)	2570	170.5 ± 9.4	170.9 ± 8.8	0.33
Higher education (%)	2765	26.1	27.1	0.63
Disease duration (years)[median, IQR]	2655	8.4 [3.1,16.3]	8.2 [2.7,15.0]	0.15
Peripheral arthritis (%)	2765	52.7	72.2	<0.001
Ever psoriasis (%)	2261	10.8	11.3	0.77
Follow-up (years))[median, IQR]	2765	4.7 [2.6,6.9]	6.0 [3.8,7.9]	<0.001
HLA-B27 *(% positive)*	2321	67.0	62.1	0.046
CRP at baseline (mg/l))[median, IQR]	1642	7.0 [2,10]	6.0 [3,11]	0.12
Ever Smoker (%)	2542	60.0	56.3	0.13
MNYC positive (%)	1909	71.0	67.6	0.19
ASAS axSpA positive (%)	2152	80.6	65.3	<0.001
BASDAI	2100	5.04 ± 1.94	5.10 ± 1.89	0.58
BASFI	2090	3.78 ± 2.35	4.01 ± 2.42	0.07
ASDAS-CRP	1972	3.08 ± 0.93	3.17 ± 0.85	0.10
TNFi :				
Infliximab (%)	722	23.3	37.2	<0.001
Adalimumab (%)	922	34.4	29.0	0.02
Etanercept (%)	759	28.5	23.2	0.01
Golimumab (%)	339	13.0	9.5	0.03
Certolizumab (%)	23	0.8	1.1	0.50
TNFi discontinuation (N):		1006	272	0.20
Adverse events (n, %)		244 (24.3)	68 (25.0)	
Remission (n, %)		32 (3.2)	16 (5.9)	
Other reasons (n, %)		253 (25.1)	65 (23.9)	
Ineffectiveness (n, %)		477 (47.4)	123 (45.2)	

Table 2. Change in BASDAI and ASDAS-CRP scores after 1 year of treatment with TNFi in patients with axSpA classified by TNFi monotherapy versus co-therapy in the different subgroups.

	BASDAI				ASDAS-CRP			
	N	Mono	Comb	P	N	Mono	Comb	P
All treatment courses	1928	-2.02	-2.00	0.83	1967	-1.14	-1.12	0.45
ASAS criteria positive	1215	-2.05	-2.15	0.29	1248	-1.15	-1.21	0.22
MNYc positive	1042	-2.03	-2.10	0.45	1093	-1.16	-1.20	0.42
nr-axSpA	151	-1.98	-1.96	0.92	174	-1.09	-1.16	0.53
1st TNFi	1365	-2.15	-2.17	0.82	1446	-1.22	-1.20	0.64
IFX patients	503	-2.01	-2.08	0.50	514	-1.10	-1.19	0.21
Peripheral involvement	1081	-2.01	-1.96	0.49	1091	-1.13	-1.09	0.39
1st TNFi and MNYc pos	738	-2.21	-2.29	0.52	792	-1.27	-1.28	0.75

Table 3. Response rates after 1 year of treatment with TNFi in patients with axSpA classified by TNFi monotherapy versus co-therapy including all treatment courses.

	N	Monotherapy	Co-therapy	P
BASDAI50	1928	28.6	25.0	0.11
BASDAI50 LUNDEX		19.0	18.6	
ASDAS-CII	1563	50.7	51.7	0.73
ASDAS-CII LUNDEX		33.7	38.5	
ASDAS-ID	1913	15.1	9.5	0.01
ASDAS-ID LUNDEX		10.0	7.1	
ASAS20	1896	84.5	83.8	0.76
ASAS 20 LUNDEX		56.2	62.3	
ASAS40	1896	19.8	19.1	0.77
ASAS 40 LUNDEX		13.2	14.2	

Characteristic	Monotherapy N=379	Co-therapy N=379	*p*
Age (years)	46.5 ± 12.2	44.4 ± 12.7	0.01
Gender (%, male)	57.3	58.3	0.83
Weight (kg)	73.5 ± 15.2	74.8 ± 16.0	0.33
Height (cm)	169.7 ± 9.5	170.8 ± 8.4	0.10
Higher education (%)	23.0	22.4	0.93
Disease duration (years)[median, IQR]	9.6 [3.2 ; 17.3]	8.9 [3.6 ; 17.3]	0.93
Peripheral arthritis (%)	77.7	78.8	0.77
Follow-up (years) [median, IQR]	2.5 [0.8 ; 5.4]	2.4 [0.9 ; 5.7]	0.75
HLA-B27 *(% positive)*	65.3	71.0	0.13
CRP at baseline (mg/l))[median, IQR]	8.0 [4.0; 18.0]	8.0 [4.0; 19.0]	0.61
Ever Smoker (%)	58.0	56.7	0.76
MNYC positive (%)	69.6	72.9	0.42
ASAS axSpA positive (%)	53.0	66.5	<0.001
BASDAI	5.0 ± 2.5	4.7 ± 2.3	0.18
BASFI	4.0 ± 2.5	3.9 ± 2.6	0.85
ASDAS-CRP	3.8 ± 1.0	3.7 ± 1.0	0.29
Infliximab (%)	44.1	36.2	0.03
Adalimumab (%)	21.6	28.0	0.053
Etanercept (%)	24.0	26.9	0.40
Golimumab (%)	10.3	10.3	1.00
Certolizumab (%)	1.1	0.8	1.00

Supplementary Table 1. Baseline characteristics of patients with axSpA classified by treatment with TNFi monotherapy verses TNFi in association with a csDMARD (co-therapy) in the propensity matched sample. Except where indicated otherwise, values are the mean (± standard deviation). N = number. TNFi = tumour necrosis factor inhibitor; axSpA = axial spondyloarthritis; IQR = Inter Quartile Range; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using CRP (C-reactive protein) levels.

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